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Remarks:

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(54) **External ultrasound apparatus for enhancement of thrombolysis**

(57) Apparatus and methods are provided for en-
hancing the thrombolytic action of a thrombolytic agent
and removing a thrombosis from a vascular system by
introducing a select dose of thrombolytic agent proxi-
mate the thrombosis disposed within a vessel of a body
and radiating the thrombosis with ultrasound generated

exterior to the body to effect removal of the thrombosis
in less time than the time required by activity of the se-
lected dose of thrombolytic agent without the ultrasonic
radiation of the thrombosis.

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Description

[0001] The present invention is generally related to an apparatus producing ultrasonic energy and is more particularly directed to an ultrasound apparatus in combination with thrombolytic agents to dissolve arterial thrombi.

[0002] It has been demonstrated that the utilization of ultrasonic waves can improve the diffusion and penetration of medicinal fluids or the like into the vascular system (see U.S. Patent No. 5,197,946 to Tachibana). Tachibana teaches that in order to effectively enhance or improve the diffusion and penetration of a medicinal fluid, the oscillating element must be disposed at the point of injection of the medicinal fluid.

[0003] This is to be contrasted, according to Tachibana, with prior art techniques which utilize ultrasonic waves for improved diffusion and penetration of medicinal fluids in which the ultrasonic oscillating element is located outside the body and far from the distal end of the catheter wire which has difficulty in exhibiting a sufficient effect due to the damping of ultrasonic energy in the course of transmission down the catheter.

[0004] Other disadvantages in the use of a transmission wire to deliver ultrasonic energy to a thrombosis is transmission wire stiffness.

Further, as the transmission wire diameter is reduced to lower the stiffness thereof, it is more difficult to deliver sufficient energy for effective removal of the thrombosis. To overcome these disadvantages, miniature ultrasonic ablation tools have been developed, utilizing ultrasonic transducers sized for arterial insertion. While these devices overcome the transmission wire difficulties, their small size severely limits the amount of ultrasonic energy available for direct mechanical action for fragmenting plaque and thrombosis and/or energy from improving diffusion and penetration of medicinal fluids as described in U.S. Patent No. 5,197,946.

[0005] Ultrasonic apparatus has also been utilized to assist in the delivery of medicaments in specific areas of a vein. For example, U.S. Patent No. 5,040,537 to Katakura teaches the use of injecting numerous fine capsules, with an agent being packed therein, into a patient's body and thereafter applying a shock wave to provide dominant positive pressure from outside the body to rupture the capsules dispersed in the body.

[0006] Thus, ultrasonic energy in the form of a pulsed shock wave is generated exterior to the body and imaged to selectively burst agent-containing capsules in order to selectively release the agent into the blood.

[0007] WO-A-9315670 discloses an apparatus for removal of cardiovascular blockage comprising several ultrasound transmitters having a power output of about 3 W/cm². This document also discloses that a person having an acute infarct should get intravenous treatment with medicine as soon as possible.

[0008] However, none of the teachings have recognized a long range, ultrasonic effect on drug effectiveness. The present invention is directed to the discovery that drug effectiveness within a vessel can be enhanced through the use of ultrasonic energy generated exterior to a body containing the vessel.

SUMMARY OF THE INVENTION

[0009] The present invention provides an apparatus as claimed in claim 1. The present invention utilizes the discovery of long range ultrasonic effects on drug effectiveness. Particularly, the present invention provides an apparatus for increasing thrombolytic action of a thrombolytic agent by radiating a thrombolytic agent and thrombosis disposed within the body vessel with ultrasound generated exterior to the body vessel.

[0010] Importantly, this step can be carried out during thrombolytic action by the thrombolytic agent on the thrombosis disposed within the body vessel.

[0011] This apparatus is clearly distinguished from the prior art such as taught by Katakura in U.S. Patent No. 5,040,537, in which ultrasound generated exterior to the body vessel is used only to rupture capsules containing an active agent. Clearly, the prior art is specifically directed to the release of an active agent within a vessel, whereas the present invention is directed to enhancing, or increasing, the effect of the thrombolytic agent during its activity in dissolving, or splitting up, a thrombus. In other words, the present invention involves a phenomena of long range ultrasound enhancement of inherent drug activity.

[0012] The present invention enables the enhancement, or acceleration, of the activity of an thrombolytic agent and in that regard enables the steps of introducing a selected dose of thrombolytic agent proximate to a thrombosis disposed in the vessel of a body and radiating the thrombosis with ultrasound generated exterior to the body to effect removal of the thrombosis in less time than required by activity of the selected dose of thrombolytic agent without ultrasound radiation of the thrombosis.

[0013] In other words, the apparatus of the present invention for enhancing thrombolytic action of a thrombolytic agent enables the steps of injecting a thrombolytic agent proximate a thrombosis disposed in a vessel within a body and directing ultrasonic energy generated exterior to the body, at the thrombosis, with proximate thrombolytic agent, of sufficient energy to increase the thrombolytic action of the thrombolytic agent.

[0014] The apparatus of the present invention is capable of removing a cardiovascular obstruction, including the steps of delivering a thrombolytic agent proximate a cardiovascular obstruction disposed in a vessel within a body and

directing ultrasonic energy, generated exterior to the body, at the cardiovascular obstruction with proximate thrombolytic agent, of sufficient energy to remove, in combination with the thrombolytic agent, the cardiovascular obstruction from the vessel.

[0015] More particularly, in accordance with the present invention, the thrombolytic agent is streptokinase in a concentration of about 250 µg/ml.

[0016] Additionally, the radiation by ultrasound may include continuous or pulsed radiation.

[0017] The discovery, leading to the apparatus in accordance with the present invention as herein described, that ultrasonic energy, or ultrasound, can have a profound effect on the activity of a drug at "long range", has heretofore been unappreciated by workers in the field as represented by the hereinabove discussed prior art.

[0018] Clearly, the prior art teaches away from this discovery since prior art workers only were able to obtain enhancement for release of drugs within a vessel by proximate introduction of ultrasound, which was thought to be due to mechanical agitation of surrounding vessel walls, as pointed out by Tachibana in U.S. Patent No. 5,197,946. It must be accepted that the mechanism taught by the Tachibana reference is not applicable to the present discovery in which it has been found that the "long range" radiation of the vessels from a point exterior to the vessel and body containing same enhances drug effectiveness.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The advantages and features of the present invention will be better understood by the following description when considered in conjunction with the accompanying drawings in which:

Figure 1 is a diagram of ultrasonic surgical apparatus in accordance with the present invention for removing a thrombosis, as well as enhancing the thrombolytic action of a thrombolytic agent;

Figure 2 is a representation of an aorta having bilateral thrombosis induced in iliofemoral arteries; and

Figure 3 is a representation similar to that shown in Figure 2 after one of the thrombi in the iliofemoral arteries has been removed in accordance with the apparatus and method of the present invention.

DETAILED DESCRIPTION

[0020] Turning now to Figure 1, there is shown apparatus 10 in accordance with the present invention for both removing a thrombosis and for enhancing thrombolytic action of a thrombolytic agent which may include a vial 12 of a thrombolytic agent which, by way of a valve 14 and a catheter 16, provides a means for injecting, introducing and delivering the thrombolytic agent to a vessel 18 within a body 20 proximate a thrombosis 22 illustrated by the dashed lines in Figure 1.

[0021] Alternatively, the thrombolytic agent can be introduced or injected into the vessel 18 proximate the thrombosis in any conventional manner, including, for example, hypodermic needle or the like (not shown). Also shown in Figure 1 is a transducer 28 having a tip positioned exterior to the body 12 and interconnected to an oscillator/driver 34 which provides means for radiating the cardiovascular blockage 30 with proximate thrombolytic agent from a position exterior to the vessel 18 and body 20.

[0022] The ultrasonic transducer 28 may be of any conventional design with a frequency range of about 19 to about 1 MHz, the frequency being manually adjustable for transmitting ultrasonic frequency through a tip 30. The frequency range may be limited to a range of between about 20 kHz and about 500 kHz if desired.

[0023] It should be appreciated that the tip 30 can include means for focusing the ultrasound as may be required in order to concentrate or specifically direct the ultrasound to a desired area or volume.

[0024] The driver is powered through conventional 110 volt line 38 and has a power output of about 50 watts through a tip active area of about 1.9 cm by 1.9 cm (about 0.75 inches by 0.75 inches) i.e. about 3.6 cm². The power levels obtainable from the ultrasonic transducer 28 are capable of producing violent cavitation in tap water at atmospheric pressure and the limiting factor of introducing ultrasonic power into the body 20 would be possible skin irritation despite the output capability of the device. The driver 34 and transducer may be operated at a duty cycle of 100%, i.e., continuous output, or pulse-operated at, for example, a 50% duty cycle.

[0025] In accordance with the present invention, the apparatus 10 is useful for removing a thrombosis in which a selected dose of thrombolytic agent is introduced proximate the thrombosis disposed within a vessel 18 in the body 20 and a thrombosis 22 is radiated with ultrasound generated exterior to the body 20 to effect removal of the thrombosis in less time than required by activity of the selected dose of thrombolytic agent, without the ultrasound radiation of the thrombosis. Specific examples of a method will be shown in the following examples.

[0026] A method includes the introduction of streptokinase as a thrombolytic agent into the vessel 18. As will be specifically set forth in the examples, the ultrasound may be continuously introduced or introduced in pulses, whereas the streptokinase may be introduced at concentrations of less than about 2,000 µg/ml. The apparatus of the invention

includes streptokinase in a concentration of about 250 µg/ml.

[0027] In some instances, the apparatus of the present invention not only provides enhancement, or acceleration, of the activity of the thrombolytic agent but also provides for removal of a thrombosis, utilizing a combination of the exterior radiated ultrasound and thrombolytic agent, which otherwise cannot be removed through the use of a thrombolytic agent by itself. This is specifically set forth hereinafter in the following examples.

Example I

Experimental Setup

[0028] Ultrasound device, Piezo driver, Model CU51 - E -001, was produced by PIEZO Systems, Inc., Cambridge, Massachusetts. The frequency of the machine is about 26 kHz. The transducer's overall dimensions are 6.5 cm in length and 2.0 cm in diameter. The output of ultrasound energy can be adjusted by turning both the amplitude knob and frequency knob. The output of ultrasound energy can be measured by watching the Power Meter (unit: microamperes). There are no direct meters to reflect the operating frequency and operating ultrasound intensity.

Results

[0029] About 200 clots from a health researcher were used in serial in vitro studies to confirm that external ultrasound can enhance the thrombolytic action of a thrombolytic agent such as streptokinase. The results are as follows:

Clot reduction is dependent on the dosage of streptokinase. The effects of three different concentrations of streptokinase (SK) (50 µg/ml, 250 µg/ml, 2,000 µg/ml) and ultrasound on one-hour old clot lysis were analyzed for thirty minutes. The results are shown in Table 1 for an ultrasound device at a power level of about 20 microamperes (pulsed mode), 40 microamperes (continuous mode), and in Table 2 for streptokinase alone.

[0030] It can be seen by comparison of Tables 1 and 2 that for a given dose of streptokinase, a significantly greater reduction in clot size (by weight percent) occurs when the clot is radiated with ultrasound for an equal period of time, 30 minutes. Therefore, a shorter length of time is required for a desired clot reduction when both ultrasound and the streptokinase are utilized as opposed to streptokinase itself.

Table 1

	USD+SK (50 µg/ml)	USD+SK (250 µg /ml)	USD+SK (2000 µg /ml)
reduction, %	63%	81%	85%
weight reduction	170 mg	262 mg	315 mg

Table 2

	SK (50 µg /ml)	SK (250 µg /ml)	SK (2000 µg /ml)
reduction, %	26% (n=2)	29±6% (n=7)	48% (n=2)
weight reduction	48±4 mg	74±24 mg	130±28 mg

Example II

[0031] Utilizing the sample experimental setup as in Example I, the function of clot reduction on ultrasound exposure time has been determined. With the combination of streptokinase (250 µg/ml) and ultrasound, one-hour old clot lysis were tested, using four different exposure times, 5 minutes, 10 minutes, 13 minutes and 30 minutes. The results are shown in Table 3.

Table 3

	Clot reduction rate	Clot weight reduction
5 minutes subgroup (n=1)	30%	30 mg
10 minutes subgroup (n=2)	30±16%	36±9 mg
15 minutes subgroup (n=8)	46±9%	126±33 mg
30 minutes subgroup (n=8)	68±9%	211±33 mg

Example III

[0032] Utilizing the same experimental setup as in Example I, the function of clot reduction on clot age has been determined, with 250 µg/ml streptokinase, combined with ultrasound for 30 minutes. The effect of clot age on thrombolysis is shown in Table 4.

Table 4

	Clot reduction %	Clot weight reduction
1-hour old clot (n=6)	74±9%	217±35 mg
2-hour old clot (n=5)	68±9%	204±27 mg
3-hour old clot (n=2)	67±4%	184±14 mg

Example IV

[0033] Utilizing the same experimental setup as in Example I, the function of thrombolysis on different clot weights has been determined with 250 µg/ml streptokinase, combined with ultrasound for 30 minutes. The effects of 1-hour old clot weight and mass on thrombolysis is shown in Tables 5 and 6.

Table 5

In lighter clot subgroup (90-126 mg):	Clot reduction %	Clot weight reduction
SK + USD (n=13)	78±14%	82±12 mg
SK alone (n=2)	35±4%	55±14 mg

Table 6

In heavier clot subgroup (228-357 mg):	Clot reduction %	Clot weight reduction
SK + USD (n=13)	71±8%	215±34 mg
SK alone (n=2)	30±5	90±25 mg

Example V

[0034] Utilizing the same experimental setup as in Example I, the effect of ultrasound mode on thrombolysis has been determined. With 250 µg/ml streptokinase, the one-hour old clots were exposed to continuous and pulsed ultrasound for 30 minutes. The effect of different ultrasound modes on thrombolysis is as follows:

Continuous mode:	The average clot reduction was 78±18% (net reduction of the clot weight was 80±15 mg, n=8).
Pulsed mode:	The average clot reduction was 78±8% (net reduction of the clot weight was 84± mg, n=5).

Example VI

[0035] The experimental setup as in Example I has been utilized to perform experiments on two rabbits for evaluating an apparatus of the present invention which utilizes external ultrasound to remove arterial thrombi. As illustrated in Figure 2, arterial occlusions 42, 44 were induced in bilateral iliofemoral arteries 46, 48 communicating with the aorta

50. The occlusions 42, 44 were formed by a combination of balloon abrasion followed by electrical induction of a thrombus by a guide wire (not shown). The bilateral iliofemoral thrombi were created after fifteen minutes of electrical energy to the iliofemoral arteries and the bilateral iliofemoral occlusions so formed were documented by X-ray angiography.

5 **[0036]** After formation of the occlusions, the rabbits were given low doses of streptokinase, of about 25,000 units per kilogram of rabbit weight.

[0037] Thereafter, each rabbit was exposed to ultrasound applied over the region of the iliofemoral artery occlusion by external application to the rabbit.

10 **[0038]** Both continuous ultrasound and pulsed wave ultrasound were utilized with the pulsed wave ultrasound having a duty cycle of about 30 milliseconds.

[0039] Utilizing X-ray confirmation, only one occlusion 48 in iliofemoral artery was radiated by ultrasound with the other occlusion 42 in the other iliofemoral artery not being exposed to the ultrasound. After 37 minutes, at a power level of up to about 40 microamperes, the left iliofemoral thrombosis 44 exposed to the external ultrasound was completely dissolved, as illustrated in Figure 3. In contrast, the unexposed right iliofemoral artery 46 remained totally occluded.

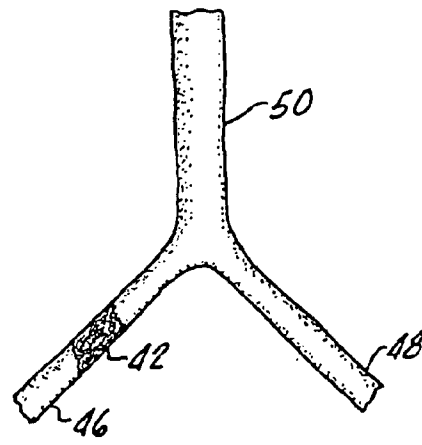
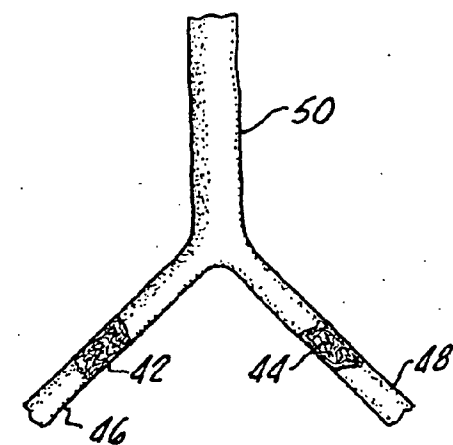
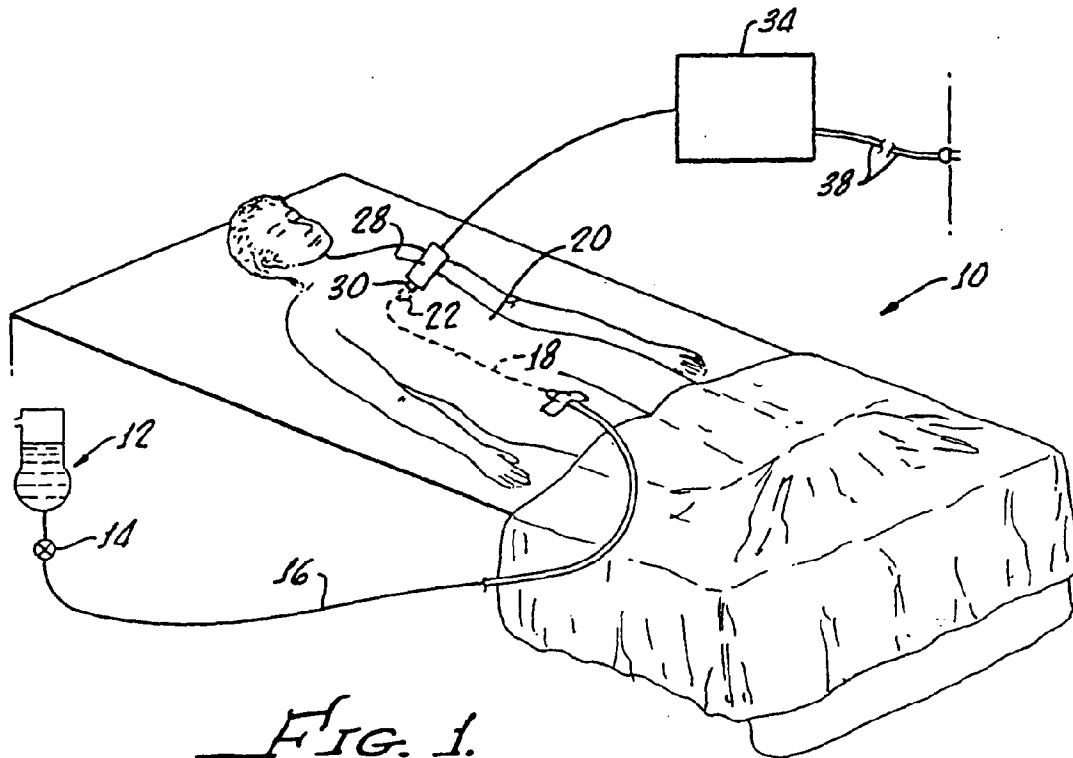
15 **[0040]** The same results were obtained through pulsed ultrasonic radiation except that a time of 40 minutes was required to totally remove the occlusion 44 from the artery 48, while the artery 46 remained occluded.

20 **[0041]** Although there has been hereinabove described a specific arrangement of ultrasonic apparatus in accordance with the present invention and a method for thrombi dissolution for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claim.

25 **Claims**

1. Apparatus for removal of a cardiovascular blockage, said apparatus comprising, in combination:

30 means for introducing a thrombolytic agent proximate a cardiovascular blockage disposed in a vessel within a body; and
ultrasonic means for radiating the cardiovascular blockage with proximate thrombolytic agent with a frequency of less than about 100 kHz at less and 50 watts of power, said ultrasonic means being disposed exterior to the vessel and body.





European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 02 01 0703

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 93 15670 A (OLSSON BERTIL) 19 August 1993 (1993-08-19) * abstract * * page 5, line 21 - line 37 * * page 6, line 5 - line 12; figure 3 * -----	1	A61N7/00
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X	EP 0 340 422 A (WOLF GMBH RICHARD) 8 November 1989 (1989-11-08) * column 3, line 5 - line 55; figure 3 * -----	1	
X	EP 0 332 871 A (DORNIER MEDIZINTECHNIK) 20 September 1989 (1989-09-20) * abstract * -----	1	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	OLSSON S B ET AL: "Enhancement of thrombolysis by ultrasound." ULTRASOUND IN MEDICINE & BIOLOGY. ENGLAND 1994, vol. 20, no. 4, 1994, pages 375-382, XP002201796 ISSN: 0301-5629 * the whole document * -----	1	A61N A61M A61B
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 11 June 2002	Examiner Moers, R
CATEGORY OF CITED DOCUMENTS X: particularly relevant: if taken alone Y: particularly relevant: if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document		T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1523 (03-02) (P447-01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82